

REMARKS

Claims 1, 4-8, 11, 14, 19-21, 24, 28-30 and 35-40 are pending in the present case. In the Final Office Action dated November 12, 2010, the Examiner re-asserted rejection of Claims 1, 4-8, 11, 14, 19-21, 24, 28-30, and 35-40 under 35 U.S.C. §103, as allegedly being unpatentable over Lapidus, *et al.*, (US 6,143,529; 11/7/00) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

Applicants disagree with the rejections for the reasons made of record in the responses filed on June 1, 2010 and October 18, 2010, which are incorporated here by reference. Further, in the amendment and response filed on June 23, 2011, Claims 1, 14, and 24 were amended to recite that nucleic acid fragments are amplified from "heterogeneous DNA isolated from supernatant from a centrifuged sample comprising a stool sample and buffer, wherein said heterogeneous DNA comprises human DNA that has not been specifically isolated from other DNA in said supernatant." The remaining claims under examination depend from Claim 1, 14, or 24, and thus also comprise this feature.

As discussed in the Amendment and Response filed on June 23, 2011, it is well known in the art that stool samples contain a mixture of human DNA and other, non-human DNA. In DNA purified from stool samples, the human DNA typically represents less than about 5% of the total DNA. See, *e.g.*, Jin, *et al.*, Molecular approaches for colorectal cancer screening, European Journal of Gastroenterology & Hepatology 10:213-217(1996), at page 214, col. 2 (provided on June 23, 2011).

Lapidus does not teach or suggest analysis of DNA fragments amplified directly from heterogeneous DNA that comprises human DNA that has not been specifically isolated from other DNA in said supernatant. Rather, as discussed in the Response of October 18, 2010 at page 8, Lapidus particularly emphasizes the difficulty of detecting cancer indicia in the heterogeneous environment of a stool sample. Thus, Lapidus teaches that, *prior to amplification*, the human DNA to be amplified *is purified* from the heterogeneous population of molecules by *sequence-specific hybrid capture*. See, *e.g.*, col 10 lines 29-30. Thus, Lapidus does not disclose amplification directly from heterogeneous DNA comprising human DNA that has not been specifically isolated from

other DNA in the supernatant, *i.e.*, in which the majority of the DNA present is non-human DNA.

The Examiner asserts that the teachings of Lapidus regarding amplified fragments of greater than 200 bp or greater being indicative of cancer, and fragments of less than 200 bp being indicative of apoptosis is "fully in line with what is disclosed in the instant specification." Office Action page 3. As a first matter, Applicants note that Lapidus consistently teaches "greater than 200," not "200 bp or greater". More importantly, Applicants respectfully point out that the relevant inquiry is what is present in the instant claims, not what similar information might be shared between Lapidus and the instant specification. The instant specification, while it discusses the value of analyzing DNA of greater than 200 bp in length in distinguishing DNA from cancer vs. apoptosis in "**additional** disease testing" (see, *e.g.*, ¶[0038]), the primary focus of the specification is on the information value of determining a total amount of patient DNA (whether from cancer cells or apoptotic cells) in a stool sample by analyzing *smaller* fragments of DNA (*i.e.*, 200 or fewer bp in length) as an initial determination of the presence of disease. See, *e.g.*, ¶[0005] and [0010]. As such, the claims of the instant case are directed to measuring the amount of DNA fragments having length of 200 bp or less, which is not "in line" with or disclosed in the teachings of Lapidus.

The Examiner has asserted that the deficiency in Lapidus with respect to measurement of genome equivalents is made up in the teachings of Hromadnikova *et al.* (Office Action, page 5). While Hromadnikova does teach determination of "genome equivalents", the teachings of Hromadnikova are not sufficient to make up for all of the deficiencies of Lapidus discussed above. Hromadnikova teaches amplification of specific gene markers in maternal plasma in order to identify Down syndrome fetuses. Plasma is a wholly different sample type than stool and would not be expected to have a composition in which a substantial amount of the DNA present, *e.g.*, 95%, is from non-human sources. Hromadnikova fails to teach or suggest a method comprising the step of measuring an amount of nucleic acid fragments amplified from heterogeneous DNA isolated from a stool sample, in which the heterogeneous DNA comprises human DNA

that has not been specifically isolated from other DNA in a supernatant produced from the stool sample.

Neither Lapidus nor Hromadnikova teaches or suggests quantification of total patient DNA in a stool sample as a screening tool for making an initial determination of the presence of disease. As such, the references do not provide, nor does the Examiner articulate, any motivation for one of skill in the art to combine the genome quantitative approach of Hromadnikova with the stool sample testing of Lapidus. Furthermore, neither Lapidus nor Hromadnikova teach quantifying patient DNA in a stool sample by measuring an amount of nucleic acid fragments amplified *from heterogeneous DNA* isolated from supernatant from a centrifuged sample comprising a stool sample and buffer, *wherein said heterogeneous DNA comprises human DNA that has not been specifically isolated from other DNA in the supernatant*. As such, even if the teachings of Hromadnikova are combined with the teachings of Lapidus (Applicants do not concede that such a combination is proper or would be made by one of skill in the art), the combination fails to teach or suggest each and every feature of the instant claims.

It remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. Section 2143.03 of the MPEP, citing *See In re Wada and Murphy*, citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Lapidus and Hromadnikova does not teach or suggest all the features of Claims 1, 4-8, 11, 14, 19-21, 24, 28-30 and 35-40, and cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. If the Examiner wishes to discuss this case, Applicants encourage the Examiner to call the undersigned at 608-662-1277 at the Examiner's convenience.

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